Strategies for subacute/chronic type B aortic dissection: The Investigation of Stent Grafts in Patients with Type B Aortic Dissection (INSTEAD) trial 1-year outcome

Christoph A. Nienaber, MD, PhD,[a] Stephan Kische, MD,[a] Ibrahim Akin, MD,[a] Hervé Rousseau, MD, PhD,[e] Holger Eggebrecht, MD,[b] Rossella Fattori, MD, PhD,[f] Tim C. Rehders, MD,[a] Guenther Kundt, MD, PhD,[a] Dierk Scheinert, MD, PhD,[c] Martin Czerny, MD, PhD,[g] Tilo Kleinfeldt, MD,[a] Burkhart Zipfel, MD,[d] Louis Labrousse, MD, PhD,[h] and Hüseyin Ince, MD, PhD[a]

Objective: Endovascular stent grafting represents a novel concept for type B aortic dissection both in the acute and subacute/chronic setting, with an unknown effect on outcomes.

Methods: In a prospective trial 140 patients with stable type B dissection were randomly subjected to elective stent-graft placement in addition to optimal medical therapy (n = 72) or to optimal medical therapy (n = 68) with surveillance (arterial pressure according to World Health Organization guidelines ≤120/80 mm Hg). The primary end point was 1-year all-cause mortality, whereas aorta-related mortality, progression (with need for conversion or additional endovascular or open surgical intervention), and aortic remodeling were secondary end points.

Results: There was no difference in all-cause mortality: cumulative survival was 97.0% ± 3.4% with optimal medical therapy versus 91.3% ± 2.1% with thoracic endovascular aortic repair ($P = .16$). Moreover, aorta-related mortality was not different ($P = .42$), and the risk for the combined end point of aorta-related death (rupture) and progression (including conversion or additional endovascular or open surgical intervention) was similar ($P = .86$). Three neurologic adverse events occurred in the thoracic endovascular aortic repair group (1 paraplegia, 1 stroke, and 1 transient paraparesis) versus 1 episode of paraparesis with medical treatment. Finally, aortic remodeling (with true-lumen recovery and thoracic false-lumen thrombosis) occurred in 91.3% with thoracic endovascular aortic repair versus 19.4% with medical treatment ($P < .001$), which is suggestive of continued remodeling.

Conclusions: In survivors of uncomplicated type B aortic dissection, elective stent-graft placement does not improve 1-year survival and adverse events, despite favorable aortic remodeling. (J Thorac Cardiovasc Surg 2010;140:S101-8)

Endovascular stent-graft repair is considered life-saving in patients with complicated type B aortic dissection, contained rupture, or organ malperfusion syndrome,[1-3] yet stable patients are traditionally managed conservatively (annual survival ≥80%). However, long-term outcomes remain sobering because of potential false-lumen expansion.[4-6] The idea that membrane-coated stents might improve the prognosis in patients with subacute/chronic type B dissection has been proposed.[6]

Although traditional management has focused on open surgical intervention or medical management, endovascular repair of aortic dissection is possible.[1,2,7-10] However, there is ongoing debate regarding clinically stable type B aortic dissection, with current consensus in support of surveillance and tight control of hypertension.[7,11,12] Reports showing both 30% mortality at 2 years[6] and less than 50% long-term survival[12] have made thoracic endovascular aortic repair (TEVAR) seem attractive as a possible alternative.

MATERIALS AND METHODS

Study Design

Methodological aspects of the comparative trial have been described previously.[6] The rationale was to compare conservative with endovascular interventional treatment prospectively with regard to their effect on improved outcomes.[4,13-15]

The study protocol was approved by the human rights and ethics committee at the coordinating center and by the local institutional review board at each participating center. An independent data and safety monitoring

From the Divisions of Cardiology and Biomedical Statistics,[a] University of Rostock, Rostock, Germany; University of Duisburg–Essen,[b] Essen, Germany; University Heart Center Leipzig,[c] Leipzig, Germany; German Heart Institute Berlin,[d] Berlin, Germany; the Centre Hospitalière Universitaire,[e] Hôpital de Rangueil, Toulouse, France; the Universitá St. Orsola Malpighi,[f] Bologna, Italy; and the Department of Cardiothoracic Surgery,[g] University of Vienna, Vienna, Austria; and Bordeaux Heart University Hospital,[h] Bordeaux, France.

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Address for reprints: Christoph A. Nienaber, MD, PhD, Department of Internal Medicine, Division of Cardiology, University of Rostock, Ernst-Heydemann-Str. 6, 18055 Rostock, Germany (E-mail: christoph.nienaber@med.uni-rostock.de).

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TABLE 1. Baseline characteristics of the patients

Characteristics	Medical therapy (n = 66)	Medical therapy plus stent graft (n = 70)	*P* value
Age, y	59.9 ± 11.6	60.3 ± 10.6	.84*
Male sex, no. (%)	54 (81.8)	60 (85.7)	.64†
Atherosclerosis/hypertension, no. (%)	54 (81.8)	59 (84.3)	.82†
Marfan syndrome, no. (%)	0 (0)	2 (2.9)	.50†
Hypertension only, no. (%)	10 (15.2)	7 (10.0)	.44†
Unknown, no. (%)	2 (3.0)	2 (2.9)	1.00†
Diabetes mellitus, no. (%)	5 (7.6)	5 (7.1)	1.00†
Active smoking, no. (%)	17 (25.8)	14 (20.0)	.54†
Pulmonary disease, no. (%)	9 (13.6)	7 (10.0)	0.60†
Body mass index	27.7 ± 5.5	26.7 ± 4.4	0.21*
NYHA classification, no. (%)			.33‡
I	51 (77.3)	55 (78.6)	
II	11 (16.7)	14 (20.0)	
III	4 (6.1)	1 (1.4)	
ASA class, no. (%)			.16‡
I (healthy status)	20 (30.3)	23 (32.9)	
II (mild systemic disease)	39 (59.1)	32 (45.7)	
III (severe systemic disease)	7 (10.6)	15 (21.4)	
Maximal diameter of dissected aorta, mm	43.5 ± 9.2	44.2 ± 9.5	.59§
Dissection morphology, no. (%)			.56†
Confined to descending thoracic aorta	5 (7.6)	8 (11.4)	
Thoracoabdominal extension	61 (92.4)	62 (88.6)	
Re-entry, no. (%)			.23‡
No	23 (34.8)	20 (28.6)	
Thoracic	14 (21.2)	8 (11.4)	
Abdominal	24 (36.4)	33 (47.1)	
Thoracoabdominal	5 (7.6)	9 (12.9)	
False lumen, no. (%)			.86†
Perfused	43 (65.2)	44 (62.9)	
Perfused with partial thrombosis	23 (34.8)	26 (37.1)	

Values are presented as means ± standard deviations where shown. *NYHA*, New York Heart Association; *ASA*, American Society of Anesthesiologists. *The *P* value was calculated by using the 2-sample *t* test. †The *P* value was calculated by using the Fisher's exact test. ‡The *P* value was calculated by using the χ^2 test. §The *P* value was calculated by using the Mann–Whitney *U* test.

board oversaw the conduct, safety, and efficacy of the trial in scheduled adjudication meetings and decided to continue the trial on the basis of an interim analysis after enrolling half the required number of patients. Data management and statistical analyses were performed by the coordinating center at the University of Rostock.

Study Population

Consecutive patients with type B aortic dissection in the subacute/chronic phase were included at 7 centers in Germany, Italy, and France. Patients were considered unsuitable for randomization in the presence of traditional indications for endovascular or open surgical intervention (diameter ≥6 cm) or in the presence of acute complications. After an interim of at least 14 days to identify early complications and exclude spontaneous false-lumen thrombosis, all patients were considered subacute or chronic cases. Randomization was carried out at a 1:1 ratio centrally by means of a computer-generated permuted-block sequence. Written informed consent was obtained.

Interventional Procedures

Individually selected stent grafts (TALENT; Medtronic, Inc, Santa Rosa, Calif) were used to scaffold up to 20 cm of dissected thoracic aorta. The procedure was performed with digital angiography and transesophageal ultrasonography. The femoral artery could usually accommodate the 24F stent-graft system, which was advanced over a 260-cm stiff wire navigated in the true lumen and deployed under rapid pacing.[16,17] Intentional coverage of the left subclavian artery (LSA) was accepted to avoid endoleak; surgical revascularization of the LSA was performed at the discretion of the operator. In the presence of a lusorian artery, incomplete circle of Willis, or dominant left vertebral artery, an LSA bypass was placed before stenting.[15,18,19]

Clinical Outcome and End Points

Clinical outcome and events were classified in accord with reporting standards of the Ad Hoc Committee for Standardized Reporting Practices in Vascular Surgery/International Society for Cardiovascular Surgery.[15,20] An outcomes adjudication committee consisting of a cardiac surgeon, 2 vascular surgeons, and 2 cardiac interventionalists assessed each complication independently in blinded fashion; potential disagreements were planned to be resolved by consensus. With serial tomographic imaging at 3 and 12 months, all patients underwent evaluation for false-lumen thrombosis and true-lumen dimensions at the level of the nondissected and dissected aorta.

Statistical Analysis

Based on previous observational evidence with an expected reduction of the primary end point from 20% to 3% to 5% in the stent-graft group, a sample size of 140 patients was required for 80% power to detect a difference, with a 2-sided α error of .05. Sample size was determined by using the study planning software nQuery Advisor 7.0 (Statcon, Witzenhausen, Germany).

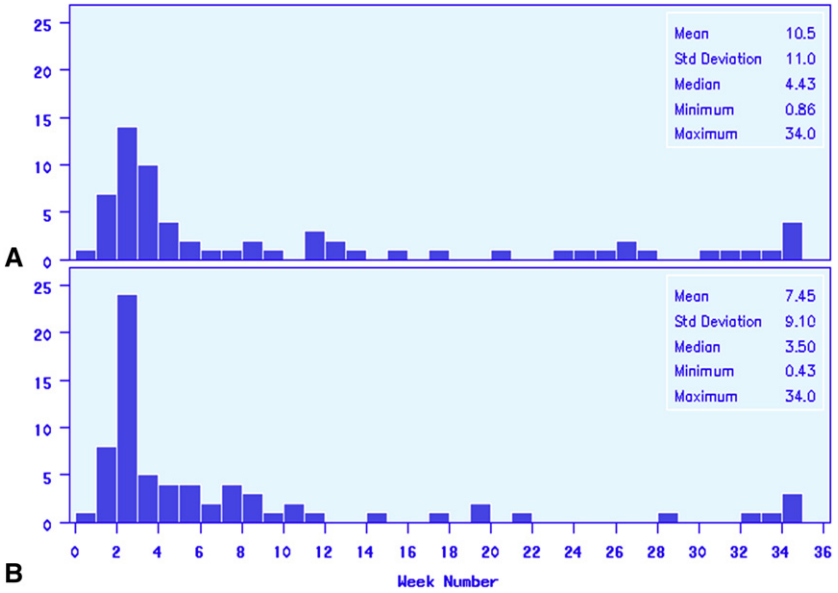

FIGURE 1. Graphic display of individual time intervals between onset of type B dissection and randomization in both groups. A, Medical treatment group; B, stent graft group.

Patients were classified according to a randomized allocation for all analyses. Data were processed with the SPSS/PC Software package version 15.0 (SPSS, Inc, Chicago, Ill). For continuous variables, differences were evaluated by use of the 2-sample *t* test or nonparametric Mann–Whitney *U* test. Categorical variables were compared by using the Fisher's exact test or χ^2 test. Time-to-event curves were calculated by using the Kaplan–Meier method and compared by using the log-rank test on an intent-to-treat basis. All tests were 2-tailed.

RESULTS

Patients' Characteristics and Treatment Assignment

Over a sample period of 2 years, 140 patients met the inclusion criteria and were randomly assigned to elective TEVAR with optimal medical therapy or optimal medical treatment alone. Two patients did not undergo stent-graft placement after randomization because of declined consent in one and sudden death in another; 2 patients eventually declined medical treatment and opted for early stent-graft placement, although they were randomized differently. Overall, 140 patients were followed in both groups, with 72 patients in the endovascular arm and 68 in the medical treatment arm on an intent-to-treat basis; all patients had protocol-guided follow-up.

Baseline and demographic characteristics, comorbidity profiles and risk factors, distribution of the American Society of Anesthesiologists classification, and dissection morphology were evenly distributed. Moreover, the time interval between onset of dissection and randomization was identical between the groups, with a median of 45 and 39 days, respectively, reflecting the early phase of chronic disease (Table 1). The median interval between randomization and stent-graft placement was 12 days (range, 4–29 days; Figure 1). Procedural details and hospital stay are shown in Table 2.

TEVAR was successfully completed in 70 patients, with no intraprocedural conversion to open surgical intervention; there were no complications related to general

TABLE 2. Procedural characteristics (medical therapy and TEVAR)

Time from dissection to stent graft, d, median (range)	82 (14–360)
General anesthesia, no. (%)	68 (97.1)
Duration of procedure, min, median (range)	108 (20–200)
Intraprocedural death, no. (%)	0 (–)
Procedural success, no. (%)	67 (95.7)
No. of stent grafts per patient, no., median (range)	1.34 (1–3)
Femoral access, no. (%)	66 (94.3)
Occlusion of LSA, no. (%)	17 (24.3)
Carotid–subclavian bypass, no. (%)	2 (2.9)
Access vessel patch repair, no. (%)	1 (1.4)
Hospital stay, d, median (range)	8 (5–29)
ICU stay, h, median (range)	23 (12–128)

LSA, Left subclavian artery; *ICU*, intensive care unit.

TABLE 3. Periprocedural outcomes (30 days)

Mortality, no. (%)	2 (2.8)
Periprocedural events	
Retrograde type A dissection, no. (%)	1 (1.5)
Rupture of iliac access vessel, no. (%)	1 (1.5)
Conversion to open surgical intervention, no. (%)	0 (–)
Ancillary procedures, no. (%)	3 (4.5)
Stenting of iliac artery	1 (1.5)
Aortic stent-graft extension	1 (1.5)
Aortic bare stent extension	1 (1.5)
Periprocedural neurologic events, no. (%)	
Paraplegia/paraparesis	2 (2.9)
Major stroke	1 (1.5)

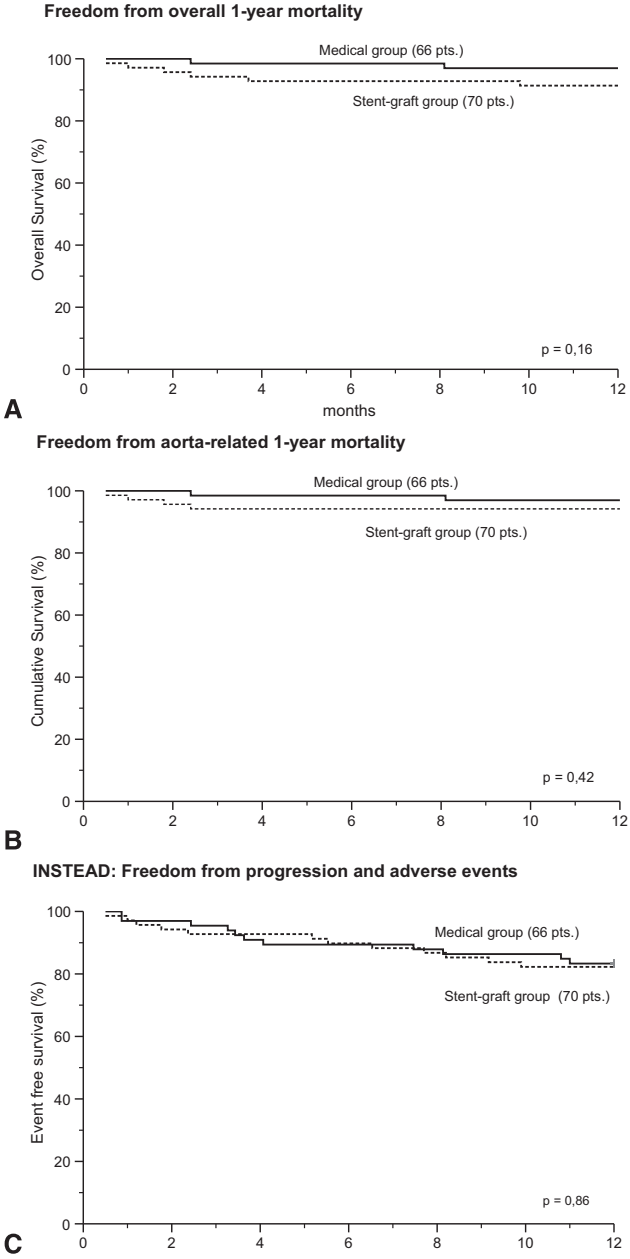

FIGURE 2. A, Kaplan–Meier estimates of 1-year overall cumulative survival in both groups ($P = .16$. log-rank test). B, Kaplan–Meier estimates of 1-year aorta-related survival in both groups ($P = .42$, log-rank test). C, Kaplan–Meier estimates of 1-year cumulative freedom from the combined end point of progression and adverse events; the combined end point consisted of related death, conversion, and ancillary interventions (including a second stent-graft procedure, access revision, and peripheral interventions). Endovascular interventions (conversion to TEVAR in the control group or additional TEVAR in the stent-graft group) are an integral part of the combined end point of progressive aortic pathology. There was no difference between groups ($P = .53$, log-rank test).

anesthesia or ventilation. A single stent graft was inserted in 58 (82.9%) patients, 2 grafts in 8 (11.4%) patients, and 3 grafts in 4 (5.7%) patients. Intentional occlusion of the LSA without prior revascularization was documented in 17 (24.3%) patients, with no neurologic sequelae or need for revascularization. Periprocedural outcomes (30 days) included 3 vascular injuries requiring ancillary procedures and 3 cases of neurologic complications with 1 paraplegia, 1 transient paraparesis in the presence of extensive coverage (3 stent grafts) with LSA occlusion (without prior revascularization), and 1 stroke. Normalized arterial pressure ($\leq$120/80 mm Hg) was documented in all patients 1 month after randomization and at follow-up visits in both groups (Table 3).

Primary Outcome

Figure 2, *A*, shows cumulative all-cause survival (estimated with the use of Kaplan–Meier curves) in both groups. Comparison between curves revealed no significant differences ($P = .16$, log-rank test). Survival probability at 1 year was 91.3% ± 2.1%% with TEVAR and 97.0% ± 3.4% with medical treatment. Unadjusted Cox regression analysis for all-cause survival revealed a hazard ratio of 0.34 with a 95% confidence interval from 0.068 to 1.670 ($P = .183$); with 9 fatalities, the death rate did not achieve the assumption of 28 events to achieve statistical power.

Secondary End Points

Figure 2, *B*, depicts freedom from aorta-related death ($P = .44$, log-rank test), with a survival probability of 94.2% ± 2.8% with TEVAR and 97.0% ± 2.1% with medical treatment alone. Analysis of individual fatalities revealed that 4 patients had been included despite protocol violations (1 acute malperfusion case on dialysis, 2 cases of acute leg ischemia, and 1 patient with ongoing pain and extra-aortic blood collection since onset of dissection).

Figure 2, *C*, illustrates the Kaplan–Meier analysis of a combined end point of aorta-related death, crossover/conversion for expansion, and ancillary procedures, revealing no differences between groups ($P = .86$, log-rank test). Cumulative freedom from the combined end point was 82.5% ± .4.7% with optimal medical treatment and 83.3% ± 4.6% with additional stent grafting.

Table 4 summarizes all events, including overall and aorta-related mortality since randomization. Aortic expansion of greater than 60 mm was more prevalent with medical treatment and followed by crossover to TEVAR in 11.2% of patients and conversion to open surgical intervention in 4.4% of patients; 1 patient crossed over for late malperfusion syndrome. There were 2 cases of ischemic spinal cord injury after stent grafting and 1 with medical therapy ($P = .91$); the latter patient had true-lumen collapse with malperfusion to various pairs of intercostal arteries 11 months after dissection, followed by late conversion to stent-graft placement. With TEVAR, all aorta-related deaths had occurred within 2 months. An additional stent graft for false-lumen expansion was required in 6 patients, whereas 3 patients converted to open surgical intervention for either expansion, retrograde type A dissection, or malperfusion. All crossover cases from medical treatment to TEVAR had an uneventful outcome, no mortality, and documented aortic remodeling.

Clinical Follow-up and Aortic Remodeling

Table 5 summarizes morphologic evolution over time in both groups and evidence of aortic remodeling. Although baseline dimensional variables were similar, placement of a stent graft was followed by expansion of the thoracic true lumen from 17.4 ± 10.7 to 25.7 ± 6.7 mm at 3 months, with further expansion to 27.1 ± 7.0 mm at 1 year ($P < .001$) at level D; similar changes were documented at level C. Simultaneously, maximal false-lumen diameter shrank from 26.9 ± 10.9 to 17.2 ± 13.7 mm at 3 months after stent grafting ($P < .001$) and to 14.6 ± 14.7 mm at 1 year at levels C and D ($P < .001$). Moreover, the process of false-lumen thrombosis in the thoracic aorta was enhanced after stent-graft placement, with 92.6% complete false-lumen thrombosis and morphologic evidence of aortic remodeling ($P < .001$), as exemplified in Figure 3. Conversely, medical treatment alone failed to demonstrate true-lumen recovery or false-lumen shrinkage from remodeling.

TABLE 4. Events within 1 year of randomization

	Medical	Stent graft	*P* value
Overall mortality, no. (%)	2 (3.0)	6 (8.6)	.28
Aorta-related mortality, no. (%)	2 (3.0)	4 (5.7)	.68
Secondary interventions, no. (%)	9 (13.6)	10 (14.3)	1.00
Crossover	7 (10.6)	0 (–)	.005
Conversion to surgical intervention	1 (1.5)	1 (1.4)	1.00
Stent-graft extension	0 (–)	5 (7.1)	.058
Aortic bare stent extension	0 (-)	1 (1.4)	1.00
PTA/access vessel repair	1 (1.5)	3 (4.2)	.62
Adverse events, no. (%)			
Persistent paraplegia/paraparesis	1 (1.5)	2 (2.9)	1.00
Major stroke	0 (–)	2 (2.9)	.50
Myocardial infarction	0 (–)	0 (–)	–

The *P* values were calculated by using the Fisher's exact test. *PTA*, Percutaneous transluminal angioplasty.

DISCUSSION

The Investigation of Stent Grafts in Patients with Type B Aortic Dissection (INSTEAD) trial showed, for the first time, that medical management for uncomplicated type B aortic dissection portends excellent survival as long as tight blood pressure control and close surveillance are ensured.[11,21,22] However, for patients not responding to medical management with progressive expansion or malperfusion, deferred endovascular therapy is feasible and safe.

Although the concept of endovascular stent grafting has been embraced to replace open surgical intervention for complicated type B dissection (even without any randomized data),[10,23,24] revelations of the INSTEAD trial do not challenge the perception of an endovascular alternative to open surgical intervention. Instead, the potential of endografting to remodel the dissected aorta[25] and address late expansion or malperfusion has been confirmed.[26] Yet TEVAR in stable low-risk patients did not improve first-year survival and was associated with spinal injury in 2.8%, as expected from previous observations.[23,24,27,28] Thus the perception that prophylactic scaffolding is a better alternative to tailored medical management has been blurred,

TABLE 5. Morphologic characteristics over time (remodeling)

Characteristics	Medical therapy (n = 66)	Medical therapy plus stent graft (n = 70)	*P* value
Baseline type B dissection			
Maximum aortic diameter	43.6 ± 9.2*	44.1 ± 9.6	.65‡
True-lumen diameter at level C	20.3 ± 9.3	19.4 ± 8.0*	.55†
False-lumen diameter at level C	27.7 ± 11.6	29.3 ± 12.4*	.65‡
True-lumen diameter at level D	17.3 ± 8.7	17.4 ± 10.7*	.91†
False-lumen diameter at level D	24.0 ± 10.4	26.9 ± 10.9*	.13†
3-mo CT follow-up			
Maximum aortic diameter	46.2 ± 11.1	44.7 ± 8.3	.75‡
True-lumen diameter at level C	21.9 ± 8.8	30.6 ± 6.0	<.001†
False-lumen diameter at level C	29.4 ± 15.0	14.0 ± 14.2	<.001†
True-lumen diameter at level D	17.1 ± 8.8	25.7 ± 6.7	<.001†
False-lumen diameter at level D	27.4 ± 12.9	17.2 ± 13.7¶	<.001†
1-y CT follow-up			
Maximum aortic diameter	45.5 ± 7.9	44.7 ± 11.9	.37‡
True-lumen diameter at level C	23.9 ± 9.9	31.8 ± 5.9	<.001†
False-lumen diameter at level C	24.7 ± 15.5	13.1 ± 18.9	<.001‡
True-lumen diameter at level D	19.3 ± 9.0	27.1 ± 7.0	<.001†
False-lumen diameter at level D	24.8 ± 11.5	14.6 ± 14.7	<.001†
False-lumen thrombosis			
Complete, no. (%)	25 (37.9)	63 (92.6)‖	<.001§
Incomplete, no. (%)	6 (9.1)	5 (7.1)	.76§

Values are presented as means ± standard deviations where shown. *CT*, Computed tomographic. **P* < .001 versus 3 months and 1 year. †The P value was calculated by using the 2-sample *t* test. ‡The P value was calculated by using the Mann-Whitney *U* test. §The *P* value was calculated by using the Fisher's exact test. ‖N = 68. ¶*P* < .001 versus 1 year (repeated-measures analysis).

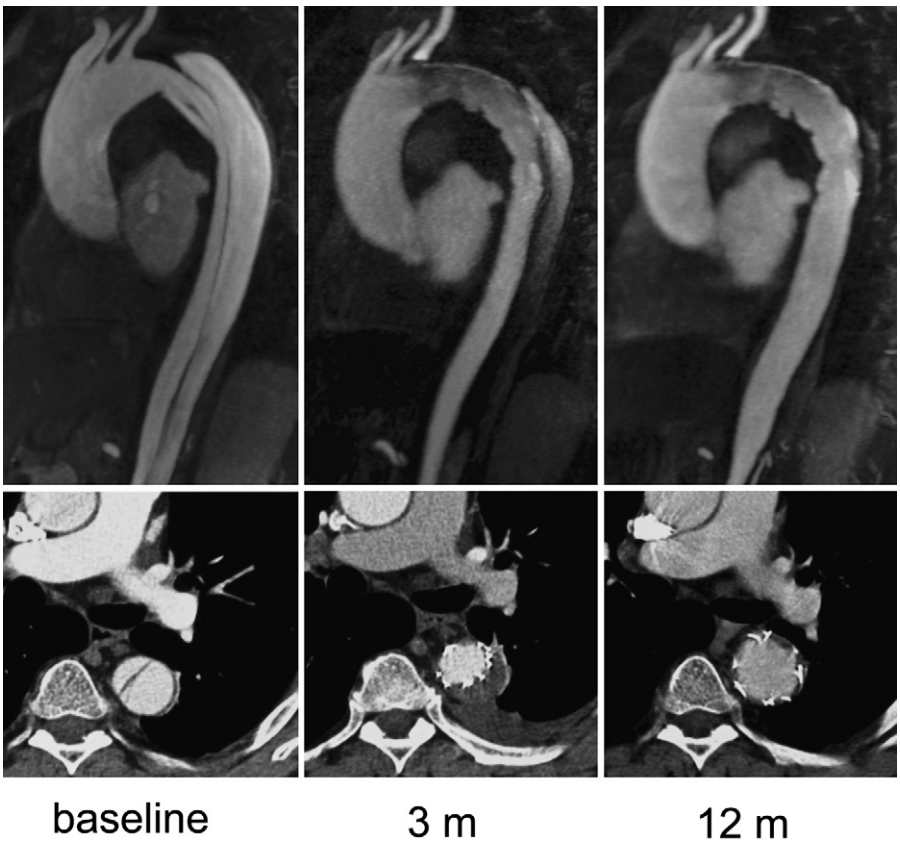

FIGURE 3. Gadolinium-enhanced sagittal magnetic resonance images of type B dissection before and after endovascular repair: serial computed tomographic transverse images demonstrate thrombosis and remodeling after stent grafting within 1 year.

given that there were some cases of expansion and late rupture that occurred regardless of therapy. Considering the benefit of carefully monitored pharmacotherapy, TEVAR appears appropriate in cases of emerging complications: all patients crossing over to TEVAR had an uneventful follow-up with remodeling despite rather late intervention.[29,30]

Thus the INSTEAD trial supports the notion of a complication-specific approach instead of TEVAR for all type B dissections. Survivors of type B dissection subjected to best medical management have an excellent outcome, but surveillance is needed to identify progression and to select patients for crossover to TEVAR or ancillary procedures.

Although the concept of prophylactic scaffolding to initiate remodeling is intriguing and intuitively promising, longer follow-up in larger cohorts is probably warranted to reveal differences. Nevertheless, the mortality observed in both the medical and endovascular groups was considerably lower than expected, a frequent observation in controlled randomized trials based on historic mortality data. Thus the INSTEAD trial calls for reappraisal of standardized care with blood pressure control and surveillance for patients with distal dissection regardless of treatment. Tailored medical management (in patients with uncomplicated type B dissection) avoids procedure-related adverse events, but patients should be followed for late complications. Nevertheless, corroborating previous findings, the INSTEAD trial confirmed that stent grafts enhance false-lumen thrombosis and aortic remodeling in 92% of cases.[25,31]

The INSTEAD trial focused on cases of uncomplicated type B dissection that reached the subacute/chronic phase, between 2 and 52 weeks of onset, with a largely heterogeneous risk profile. Improved selection algorithms might help to identify those subsets of ''stable'' patients likely to benefit from prophylactic scaffolding.[32,33] Advancing TEVAR technology and growing operator skills are likely to avoid procedure-related adverse events, thus lowering the threshold for use of TEVAR in asymptomatic patients at risk despite best medical management.[30] Our current picture of clinical care is transient, and our current views of best management will soon be dated; both might be supplanted by growing insight into disease progression in patients with ''asymptomatic'' or ''uncomplicated'' dissection. New interventional platforms and improved devices will emerge and address current stent-graft inadequacies.[34] Future trials should focus on defined subgroups to test prophylactic use of refined and dedicated endografts.

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References

1. Dake MD, Kato N, Mitchell RS, Semba CP, Razavi MK, Shimono T, et al. Endovascular stent-graft placement for the treatment of acute aortic dissection. *N Engl J Med*. 1999;340:1546-52.
2. Nienaber CA, Fattori R, Lund G, Dieckmann C, Wolf W, von Kodolitsch Y, et al. Nonsurgical reconstruction of thoracic aortic dissection by stent-graft placement. *N Engl J Med*. 1999;340:1539-45.
3. Mukherjee D, Eagle KA. Aortic dissection—an update. *Curr Probl Cardiol*. 2005;30:287-325.
4. Tsai TT, Fattori R, Trimarchi S, Isselbacher E, Myrmel T, Evangelista A, et al. Long-term survival in patients presenting with type B acute aortic dissection: insights from the International Registry of Acute Aortic Dissection. *Circulation*. 2006;114:2226-31.
5. Svensson LG, Kouchoukos NT, Miller DC, Bavaria JE, Coselli JS, Curi MA, et al. Expert consensus document on the treatment of descending thoracic aortic disease using endovascular stent-grafts. *Ann Thorac Surg*. 2008;85:1-41.
6. Nienaber CA, Zannetti S, Barbieri B, Kische S, Schareck W, Rehders TC. Investigation of STEnt grafts in patients with type B aortic Dissection: Design of the INSTEAD trial—a prospective, multicenter European randomized trial. *Am Heart J*. 2005;149:592-9.
7. Erbel R, Alfonso F, Boileau C, Dirsch O, Eber B, Haverich A, et al. Diagnosis and management of aortic dissections. *Eur Heart J*. 2001;22:1642-81.
8. Eggebrecht H, Nienaber CA, Neuhäuser M, Baumgart D, Kische S, Schmermund A, et al. Endovascular stent-graft placement in aortic dissection: a meta-analysis. *Eur Heart J*. 2006;27:489-98.
9. Nienaber CA, Ince H, Weber F, Rehders T, Petzsch M, Meinertz T, et al. Emergency stent-graft placement in thoracic aortic dissection and evolving rupture. *J Card Surg*. 2003;18:464-70.
10. Trimarchi S, Nienaber CA, Rampoldi V, Myrmel T, Suzuki T, Bossone E, et al. Role and results of surgery in acute type B aortic dissection: insights from the International Registry of Acute Aortic Dissection (IRAD). *Circulation*. 2006;114:I357-64.
11. Tefera G, Acher CW, Hoch JR, Mell M, Turnipseed WD. Effectiveness of intensive medical treatment in type B aortic dissection: a single-center experience. *J Vasc Surg*. 2007;45:1114-8.
12. Nienaber CA, Eagle KA. Aortic dissection: new frontiers in diagnosis and management: part II: therapeutic management and follow-up. *Circulation*. 2003;108:772-8.
13. Akutsu K, Nejima J, Kiuchi K, Sasaki K, Ochi M, Tanaka K, et al. Effects of the patent false lumen on the long-term outcome of type B acute aortic dissection. *Eur J Cardiothorac Surg*. 2004;26:359-66.
14. Takahashi J, Wakamatsu Y, Okude J, Kanaoka T, Sanefuji Y, Gohda T, et al. Maximum aortic diameter as a simple predictor of acute type B aortic dissection. *Ann Thorac Cardiovasc Surg*. 2008;14:303-10.
15. Onitsuka S, Akashi H, Tayama K, Okazaki T, Ishihara K, Hiromatsu S, et al. Long-term outcome and prognostic predictors of medically treated acute type B aortic dissections. *Ann Thorac Surg*. 2004;78:1268-73.
16. von Knobelsdorff G, Höppner RM, Tonner PH, Paris A, Nienaber CA, Scholz J, et al. Induced arterial hypotension for interventional thoracic aortic stent-graft placement: impact on intracranial haemodynamics and cognitive function. *Eur J Anaesthesiol*. 2003;20:134-40.
17. Nienaber CA, Kische S, Rehders TC, Schneider H, Chatterjee T, Bünger CM, et al. Rapid Pacing for better placing: a comparison of techniques for precise deployment of endograft in the thoracic aorta. *J Endovasc Ther*. 2007;14:506-12.
18. Rehders TC, Petzsch M, Ince H, Kische S, Korber T, Koschyk DH, et al. Intentional occlusion of the left subclavian artery during stent-graft implantation in the thoracic aorta: risk and relevance. *J Endovasc Ther*. 2004;11:659-66.
19. Chaikof EL, Blankensteijn JD, Harris PL, White GH, Zarins CK, Bernhard VM, et al. Reporting standards for endovascular aortic aneurysm repair. *J Vasc Surg*. 2002;35:1048-60.
20. Bolland K, Whitehead J. Formal approaches to safety monitoring of clinical trials in life-threatening conditions. *Stat Med*. 2000;19:2899-917.
21. Estrera AL, Miller CC, Goodrick J, Porat EE, Achouh PE, Dhareshwar J, et al. Update in outcomes of acute type B aortic dissection. *Ann Thorac Surg*. 2007;83:842-5.
22. Winnerkvist A, Lockowandt U, Rasmussen E, Radegran K. A prospective study of medically treated acute type B aortic dissection. *Eur J Vasc Endovasc Surg*. 2006;32:349-55.

23. Buth J, Harris PL, Hobo R, van Eps R, Cuypers P, Duijm L, et al. Neurological complications associated with endovascular repair of thoracic aortic pathology: Incidence and risk factors. A study from the European Colaborateurs of Stent/Graft Techniques for Aortic Aneurysm Repair (EUROSTAR) registry. *J Vasc Surg*. 2007;46:1103-11.
24. Fattori R, Nienaber CA, Rousseau H, Beregi JP, Heijmen R, Grabenwöger M, et al. Talent Thoracic Retrospective Registry. Results of endovascular repair of the thoracic aorta with the Talent Thoracic stent graft: the Talent Thoracic Retrospective Registry. *J Thorac Cardiovasc Surg*. 2006;132:332-9.
25. Rodriguez JA, Olsen DM, Lucas L, Wheatley G, Ramaiah V, Diethrich EB. Aortic remodeling after endografting of thoracoabdominal aortic dissection. *J Vasc Surg*. 2008;47:1188-94.
26. Duebener LF, Lorenzen P, Richardt G, Misfeld M, Nötzold A, Hartmann F, et al. Emergency endovascular stent-grafting for life-threatening acute type B aortic dissection. *Ann Thorac Surg*. 2004;78:1261-6.
27. Eggebrecht H, Lönn L, Herold U, Breuckmann F, Leyh R, Jakob HG, et al. Endovascular stent-graft placement for complications of acute type B aortic dissection. *Curr Opin Cardiol*. 2005;20:477-83.
28. MacKenzie KS, LeGuillan MP, Steinmetz OK, Montreuil B. Management trends and early mortality rates for acute type B dissection: a 10-year single-institution experience. *Ann Vasc Surg*. 2004;18:158-66.
29. Akin I, Kische S, Ince H, Nienaber CA. Indication, timing and results of endovascular treatment of type B dissection. *Eur J Vasc Endovasc Surg*. 2009;37:289-96.
30. Hagan PG, Nienaber CA, Isselbacher EM, Bruckman D, Karavite DJ, Russman PL, et al. The international registry of aortic dissection (IRAD): new insights into an old disease. *JAMA*. 2000;283:897-903.
31. Schoder M, Czerny M, Cejna M, Rand T, Stadler A, Sodeck GH, et al. Endovascular repair of acute type B aortic dissection: long-term follow-up of true and false lumen diameter changes. *Ann Thorac Surg*. 2007;83:1059-66.
32. Tsai TT, Evangelista A, Nienaber CA, Myrmel T, Meinhardt G, Cooper JV, et al. Partial thrombosis of the false lumen in patients with acute type B aortic dissection. *N Engl J Med*. 2007;357:349-59.
33. Song JM, Kim SD, Kim JH, Kim MJ, Kang DH, Seo JB, et al. Long-term predictors of descending aorta aneurysmal change in patients with aortic dissection. *J Am Coll Cardiol*. 2007;50:799-804.
34. Nienaber CA, Kische S, Ince H. Thoracic aortic stent-graft devices: problems, failure modes and applicability. *Semin Vasc Surg*. 2007;20:81-9.